

At the outset, the Patent Office objects to the Specification and the Drawings. In response, Applicants have amended the Specification to include the heading entitled "BRIEF DESCRIPTION OF THE DRAWINGS".

With respect to the drawings, Applicants have submitted herewith a Request for Approval of Drawings Changes wherein the proposed drawing changes are indicated in red. Upon approval of said drawing changes and once the present application has been allowed, Applicants will provide a formal set of drawings incorporating the approved changes at this time.

Accordingly, Applicants respectfully request that the objections be withdrawn.

In the Office Action, Claims 11-23 are rejected under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph as allegedly being indefinite. The Patent Office asserts that Claims 11-23 are allegedly indefinite with respect to the term "*lactobacilli*."

Applicants respectfully submit that the term *lactobacilli* as used throughout the Specification means the plural of the genus *Lactobacillus* and, thus, includes all species and strains that belong to the genus *Lactobacillus*. This is clearly supported by the Specification. The Specification lists a number of bacteria strains which are examples of the *lactobacilli* strain. See, Specification, page 3, lines 9-19.

Although this list does include *Leuconostoc*, Applicants believe that this one example included within the list of many others should not confuse one skilled in the art as to the meaning of the term *lactobacilli*. As is generally understood in the art, the term *lactobacilli* is understood to encompass the species of the genus term *lactobacillus*. See, Topley et al., Microbiology and Microbial Infections", page 655-657 attached hereto as Exhibit A; and Berger's Manual of Determinative Bacteriology, page 566 attached hereto as Exhibit B. Therefore, Applicants believe that the term *lactobacilli* as used throughout the Specification is clearly defined.

Accordingly, Applicants respectfully request that the rejection of Claims 11-23 under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph be withdrawn.

In the Office Action, Claims 11-23 are rejected under 35 U.S.C. § 102 and/or 103. More specifically, Claims 11-13 and 15-23 are rejected under 35 U.S.C. § 102 in view of U.S. Patent No. 5,578,302 ("302"); Claims 11-23 are rejected under 35 U.S.C. § 102 in view of U.S. Patent No. 5,494,664 ("664"); Claims 11, 14-20 and 23 are rejected under 35 U.S.C. § 102 and/or 103 in view of *Yaeshima* and *Yoshida*; and Claims 11-23 are rejected under 35 U.S.C. § 103 in view of '302 or '664 with *Yaeshima* and *Yoshida*.

Applicants respectfully submit that the anticipation and/or obviousness rejections of Claims 11-23 are improper. Of the pending claims, Claims 11, 19 and 23 are the sole independent claims. Claim 11 recites a method for the treatment or prophylaxis of mineral deficiencies in a mammal comprising the steps of enterally administering to the mammal a nutritional composition comprising *lactobacilli*. Claim 19 recites a method for increasing absorption of minerals from a diet comprising the steps of enterally administering to a mammal a nutritional composition comprising *lactobacilli*. Claim 23 recites a method for improving the absorption of minerals in a mammal comprising the steps of enterally administering to the mammal a nutritional composition comprising *lactobacilli*.

Applicants have surprisingly found, by use of an *in vitro* model, that *lactobacilli* can directly facilitate or improve the absorption of minerals, particularly calcium, by intestinal cells. It is hypothesized that this desirable effect of *lactobacilli* on the absorption of minerals is linked to the induction of acidification of the microenvironment around the intestinal cells and the bacteria in contact with the intestinal cells. Both the bacteria and the intestinal cells may participate in the induction of acidification. This localized acidification might thus play an active role in the

solubilization of minerals and therefore in the capacity of the body to assimilate them. See, Specification, page 2, lines 18-26.

With respect to the anticipation rejections in view of the '302 patent or the '664 patent, Applicants respectfully submit that the cited references fail to disclose or arguably suggest a number of features of the claimed invention. For example, the references fail to disclose that the enteral administration of a nutritional composition including *lactobacilli* can facilitate or improve absorption of minerals, such as calcium and magnesium by intestinal cells, such that mineral deficiencies in mammals can be effectively treated as required by the claimed invention.

As Applicants' noted in their Amendment filed on May 29, 2001, the '664 patent merely discloses a culture of a strain of lactic acid bacterium, including three strains of the genus *Bifidobacterium*, that are selected for their affinity for implantation in an intestinal flora. See, '664, column 1, lines 64-67. Further, the '664 patent discloses additional effects of the use of these strains, particularly as an anti-diarrhoeic. Not one of the additional effects teaches that the strains can facilitate the absorption of minerals by intestinal cells. See, '664, column 1, lines 36-42.

Further, the '302 patent merely discloses a single-specific *Lactobacillus* strain that proves to be capable of competitively displacing pathogenic bacteria, in particular *Helicobacteri pylori*, from intestinal cells. Thus, the '302 patent, like the '664 patent, fails to teach that *lactobacilli* can facilitate or improve the absorption of minerals by a mammal, such as by intestinal cells, as required by the claimed invention.

Moreover, Applicants believe that the issue with respect to the anticipation rejections in view of the '302 and '664 patents is not whether these references fail to disclose the mineral absorption features of the claimed invention but rather whether the mineral absorption features define subject matter of the claimed invention. In this regard, Applicants believe that the Patent Office has

improperly given little, if any, weight to the preamble of independent Claims 11, 19 and 23 which clearly recite such features.

Of course, the preamble can further limit the claim if such is "necessary to give meaning to the claim[s] and properly define the invention." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1781 (Fed. Cir. 1992). Contrary to the Patent Office's position, Applicants believe that the preamble of independent Claims 11, 18 and 23 clearly gives meaning to Claims 11-23 by reciting the treatment and/or mineral absorption features of the claimed invention. As previously discussed, Applicants have surprisingly found, by use of an *in vitro* model, that the administration of *lactobacilli* can directly facilitate or improve the absorption of minerals, particularly calcium, by intestinal cells such that mineral deficiencies can be effectively treated. Therefore, Applicants respectfully submit that the '302 and '664 Patents fail to disclose or arguably a number of features of the claimed invention.

With respect to *Yaeshima* and *Yoshida*, Applicants believe that these references are clearly deficient with respect to a number of features of the claimed invention. As previously discussed, independent Claims 11, 19 and 23 each relate to methods that include the step of enterally administering to a mammal a nutritional composition comprising *lactobacilli*, which includes all species and strains that belong to the genus *Lactobacillus*. Claim 11 further recites a method for treatment or prophylaxis of mineral deficiencies in a mammal. Claim 19 further recites a method for increasing absorption of minerals from a diet. Claim 23 further recites a method for improving the absorption of minerals in a mammal. As previously discussed, Applicants have surprisingly found and demonstrated that *lactobacilli* are able to directly facilitate or improve the absorption of minerals, particularly calcium, by intestinal cells.

In this regard, the enhanced mineral absorption effects of *Lactobacillus* have been found not to be linked to the presence of prebiotic fiber; not to be linked to the ability of the cell to adhere to

intestinal cells; and not to be linked to the ability of the bacteria to acidify the medium. As hypothesized, the tested strains of *Lactobacillus* can acidify the microenvironment even if they do not acidify the medium. It is these microenvironments, in direct proximity of each *Lactobacillus*, Applicants believe, that can facilitate in the absorption of minerals by intestinal cells.

This is an important distinction that Applicants believe the Patent Office has misunderstood. The phenomena of acidification of the microenvironment of a bacteria (e.g., a thin layer just around the individual bacterium itself) must not be confused with the ability of a bacteria to acidify the medium, mainly because of the bacterium's metabolism. This difference between the acidification of the microenvironment and the medium, Applicants believe, should be clearly understood by the following illustration.

It is generally known that the pathogenic bacterium *Helicobacter pylori*, the causative agent of nonerosive gastritis in man, is able to survive under the acidic conditions of the stomach because it creates a microenvironment with a pH that is supportable for it. In this regard, *H. pylori* is by no means capable of regulating the pH of the entire stomach. Thus, Applicants believe that it is the acidification of the microenvironment and not the medium by *Lactobacillus* which can facilitate the absorption of minerals.

In contrast, nowhere do *Yaeshima* and *Yoshida*, alone or in combination, teach or suggest a number of features of the claimed invention. Contrary to the Patent Office's position, nowhere do either of the references teach or suggest that the enteral administration of a nutritional composition including *lactobacilli* can facilitate or improve the absorption of minerals by a mammal, such as by the intestinal cells of the mammal, as required by the claimed invention.

For example, the *Yoshida* abstract fails to make any reference to *Lactobacillus*, let alone its desirable effects on the absorption of minerals. Moreover, it further suggests that the absorption of

calcium is least affected. This teaching is completely opposite of what the Applicants have demonstrated. As seen, for example, in Figure 2 of the Specification, Applicants have shown a particularly pronounced absorption of calcium due to *Lactobacillus*. Further, nowhere does *Yoshida* teach or suggest that the intestinal bacteria increases the absorption of minerals. In this regard, the *Yoshida* Abstract merely discloses that the gnotobiotic mice suffered no deleterious effect on the apparent absorption ratio of total calcium, phosphorus and magnesium.

With respect to *Yaeshima*, at most, this reference appears to disclose that *Bifidobacteria* and not *lactobacterium* can enhance mineral absorption. See, *Yaeshima*, Abstract. The only reference that *Yaeshima* makes to *lactobacilli* is in Figure 1. In this regard, *Yaeshima* merely recognizes that *lactobacilli* can prevent colonization of pathogens and have an effect on the stimulation of immune response. Thus, nowhere does *Yaeshima* make a correlation between *lactobacilli* and enhancing absorption of minerals as required by the claimed invention. Contrary to the Patent Office's position, the beneficial mineral absorption effects of the claimed invention are believed to be linked to the acidification of microenvironments and not "acidified milk/yogurt" as disclosed in *Yaeshima*.

Further, the clear emphasis of *Yaeshima* appears to be that the enhanced effect of mineral absorption is due to the combination of a prebiotic fiber (oligosaccharide) and *Bifidobacterium* as indicated in section 8 of this reference. In contrast, Applicants have demonstrated a direct effect of strains of *Lactobacillus* without the presence of prebiotic fiber or oligosaccharides on the efficacy or activity of cells of the intestinal tract to absorb minerals. Moreover, *Yaeshima* stresses that "some of the effects seem to be general to the genus, and other effects seems to be strain-specific or host-specific."

Contrary to the Patent Office's position, Applicants believe that *Yaeshima* and/or *Yoshida* clearly do not support substituting *lactobacterium* for *Bifidobacterium* or vice versa. Indeed, this

clearly goes against what is generally understood to one skilled in the art. In this regard, Applicants submit that *Lactobacillus* and *Bifidobacterium* are very different from one another notwithstanding the fact that both are bacteria. For example, phylogenetically and physiologically both are different as they colonize clearly distinct parts of the gastrointestinal tract and their other habitats are also clearly different. In this regard, Applicants believe that *Bifidobacterium* is closely related (e.g., phylogenetically) to the fungal genus *Mycobacterium* and not *Lactobacillus* which contains highly pathogenic species, such as *M. lepra* and *M. pneumoniae* species.

Further, *Bifidobacterium* are strictly anaerobic while *lactobacilli* are only facultative anaerobic. In this regard, *Bifidobacterium* does not produce CO<sub>2</sub> (homolactic fermentation). See, Exhibit A, page 521. In general, *Bifidobacterium* is identifiable from other bacteria including *Lactobacillus* by the detection of a specific enzyme, namely, fructose-6-phosphate phosphoketolase. See, Exhibit A, page 522.

Moreover, *Bifidobacterium* exclusively inhabits vertebrates and does not live outside a living host. Typically, they are found in sewage. See, Exhibit A, page 522. In contrast, *Lactobacillus* is widely distributed in a variety of habitats where rich carbohydrate-containing substrates are available. See, Exhibit A, page 655-656.

With respect to their probiotic effects, these are based on very distinct activities. For example, in the intestines of humans, *Bifidobacterium* colonizes the large intestine (e.g., colon) (See, Exhibit A, page 524) whereas *Lactobacillus* is mainly present in the small intestine. In this regard, the immuno-beneficial effects of *lactobacilli* are primarily due to its presence in the small intestine (mainly ileum) where many immunological processes occur as even indicated in *Yaeshima* at Figure 1. From *Yaeshima* (See, Fig. 1; Chapters 3-5), we also know that *Bifidobacterium* are mainly linked to prevention of diarrhea, constipation and supplant pathogenic bacteria from the colon. This clearly

suggests that *Lactobacillus* is most active in the ileum while the *Bifidobacterium* is most active in the colon.

Based on the evident differences between *Bifidobacterium* and *Lactobacterium*, Applicants believe that one skilled in the art would not consider these bacteria as being obvious substitutes for one another. Even if combinable with the '303 Patent and/or the '664 Patent, Applicants respectfully submit that *Yaeshima* and *Yoshida*, fail to teach or suggest a number of features of the claimed invention.

Therefore, based on the apparent differences between the cited references and the claimed invention, Applicants submit that the cited references, alone or in combination, fail to anticipate and/or render obvious the claimed invention as required by Claims 11-23. Accordingly, Applicants respectfully request that the anticipation and/or obviousness rejections be withdrawn.

For the foregoing reasons, Applicants respectfully submit that the above-identified patent application is now in a condition for an allowance and earnestly solicit reconsideration of same.

Respectfully submitted,



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